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Impact of Myopia Control Interventions on Choroidal Thickness in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Topic: This systematic review and meta-analysis evaluated whether myopia control interventions produce measurable changes in choroidal thickness (ChT) in children and adolescents with myopia compared with single-vision lenses or placebo. The primary aim was to describe patterns of ChT modulation.

Clinical Relevance: Myopia is the most common ocular disorder worldwide and is projected to affect 50% of the global population by 2050. High myopia increases the risk of complications such as myopic maculopathy and retinal detachment. Early biomarkers of treatment efficacy are critical, and ChT has emerged as a promising candidate given its rapid and bidirectional response to visual and pharmacological stimuli.

Methods: The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251144689). Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) standards, randomized controlled trials (RCTs) were included if they assessed ChT changes after myopia control interventions in pediatric populations. Searches of PubMed, Web of Science, and Scopus were completed on August 5, 2025. Two reviewers independently screened, extracted, and assessed risk of bias using the Cochrane tool. Pooled mean differences with 95% confidence intervals (CIs) were calculated, and certainty of evidence was rated with Grading of Recommendations, Assessment, Development and Evaluation.

Results: Eleven RCTs including 2190 eyes were analyzed. Repeated low-level red-light therapy induced the largest thickening (mean difference = 24.1 μm, 95% CI: 19.8–28.5; $I^2 = 77\%$). Atropine produced modest but significant effects (mean difference = 10.6 μm, 95% CI: 6.7–14.5) with high heterogeneity ($I^2 = 97\%$). Orthokeratology yielded consistent increases (mean difference = 13.3 μm, 95% CI: 9.5–17.1; $I^2 = 6\%$), while lenslet spectacles showed moderate effects (mean difference = 13.2 μm, 95% CI: 5.7–20.7; $I^2 = 0\%$). Evidence certainty was rated high for most interventions and moderate for atropine.

Conclusions: Myopia control interventions produce early, measurable increases in ChT. These findings characterize patterns of choroidal modulation, while their clinical relevance remains uncertain. Further studies integrating ChT with efficacy measures are needed.

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Myopia has become the most common ocular disorder worldwide, with its prevalence rising especially in East and Southeast Asia, making it an urgent public health concern.[1,2] Beyond refractive error, high myopia dramatically increases the risk of severe complications such as myopic maculopathy and retinal detachment, primarily due to excessive axial elongation.[3,4] As clinical research shifts from mere correction to long-term prevention, the choroid (a vascular tissue between retina and sclera) has received growing attention for its regulatory role in ocular growth.[5] Compelling experimental and clinical evidence has identified choroidal thickness (ChT) as both a sensitive biomarker and possible mediator of myopia progression.[4,6,7] Choroidal thinning is linked to myopia onset and progression, while choroidal thickening has been observed after effective myopia control interventions such as orthokeratology (OK) and low-dose atropine.[8–12] The choroid demonstrates rapid, bidirectional plasticity, thinning in response to hyperopic defocus and thickening with myopic defocus, across animal and human studies.[7,13,14] Experimental work indicates that choroidal changes can precede axial adjustments during emmetropization,[15,16] although in humans the relationship between early ChT shifts and long-term axial growth remains uncertain.

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Building on these mechanisms, several optical and pharmacological interventions have been designed to control myopia by influencing retinal image profile and ocular growth.[17,18] Orthokeratology, for instance, has proven effective for slowing myopia progression in children, likely by inducing peripheral myopic defocus and increasing ChT, especially during the first year after treatment.[12,19,20] Spectacle lenses with highly aspherical lenslets and multifocal designs have also been shown to increase ChT and slow eye growth.[21,22] Low-dose atropine, a nightly antimuscarinic drop, has robust evidence for efficacy in myopia control and is associated with significant choroidal thickening.[8,23]

Recently, repeated low-level red-light (RLRL) therapy has emerged as a promising, nonpharmacological myopia control strategy in children. Repeated low-level red-light not only reduces myopia progression but also induces clinically meaningful subfoveal choroidal thickening, with the magnitude of this effect potentially correlating with treatment efficacy.[9,24] However, the detailed morphometric and vascular mechanisms underlying choroidal changes with RLRL and other interventions remain incompletely understood, due in part to challenges in quantifying stromal and luminal compartments.[25,26] Despite advances in imaging, several methodological factors continue to influence choroidal measurements, most notably, the use of cycloplegia or mydriatics, the timing of OCT scans, and biological rhythms, particularly in pediatric populations.[23,27,28] Traditional ChT measures may not fully capture the spectrum of structural changes relevant to myopia control, and new indices such as the choroidal vascularity index are being developed for a more comprehensive assessment.[25,26]

To date, only 2 meta-analyses have specifically examined ChT changes after major myopia control interventions in children. The first focused exclusively on OK, demonstrating a significant increase in subfoveal ChT during the first month of treatment, followed by a plateau in subsequent months.[29] However, this work was limited by small sample sizes, short follow-up durations, and a lack of direct comparison with other treatment modalities. More recently, a second meta-analysis investigated the effects of low-dose atropine on ChT, finding a significant increase after 1 month but with inconsistent results at later time points, and highlighting substantial heterogeneity among studies.[30] Neither meta-analysis provided a comprehensive synthesis across multiple interventions, including lenslet spectacles and RLRL therapy, nor did they address the impact of study design or methodological variables on treatment outcomes.

Despite the growing number of myopia control strategies, important gaps remain in understanding how these interventions influence choroidal structure in children. This systematic review and meta-analysis synthesize randomized controlled trials (RCTs) reporting ChT outcomes across pharmacological, optical, and light-based treatments, with the goal of characterizing patterns of choroidal modulation rather than evaluating treatment efficacy. By integrating evidence across modalities and examining sources of heterogeneity, this study provides an updated overview of choroidal responses to myopia control interventions and identifies priorities for future research on the clinical relevance and interpretation of choroidal changes in pediatric myopia management.

Methods

Research Question and Population, Intervention, Comparator, Outcomes, Study Design Framework

This systematic review and meta-analysis were registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: [CRD420251144689]) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[31] guidelines and A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2)[32] methodological standards (Fig 1). A completed Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is available as Supplementary Material (Additional File 1, available at www.ophthalmologyscience.org). The final literature search was completed on August 5, 2025. The research question was formulated using the Population, Intervention, Comparator, Outcomes, Study design framework to ensure methodological rigor and clinical relevance. Specifically, we aimed to evaluate whether children and adolescents with myopia (population) experience changes in ChT (outcome) when treated with myopia control interventions such as RLRL therapy, low-dose atropine, aspherical or highly aspherical lenslet spectacles, and OK (intervention), compared to single-vision spectacles or placebo (comparator). Eligible studies were limited to RCTs (study design), examining established or emerging myopia control strategies. The primary outcome was the change in ChT, assessed with OCT methods across different follow-up durations. The secondary analyses considered differences in study design, intervention type, and follow-up time as potential sources of heterogeneity. By synthesizing the available evidence, this review aimed to clarify the impact of myopia control treatments on choroidal morphology and to provide clinically relevant insights to guide practice and future research.

Eligibility Criteria

Studies were excluded if they met any of the following criteria: case reports, case series, quasi-experimental designs, or uncontrolled studies; systematic or narrative reviews; or duplicate publications from the same data set. Additional exclusions were applied to studies rated as having high risk of bias or insufficient methodological rigor, as well as those with noncomparable or incomplete demographic data. Trials were also excluded if they lacked clearly defined diagnostic criteria for myopia, did not include a randomized control group (e.g., single-vision lenses [SVLs] or placebo), or failed to report ChT as an outcome. Furthermore, studies were excluded if they did not provide sufficient statistical data (such as means and standard deviations or confidence intervals [CIs]) required for quantitative synthesis in the meta-analysis. Notably, no RCTs evaluating soft multifocal contact lenses reported ChT outcomes; therefore, these interventions did not meet the eligibility criteria and were not included.

Information Sources

A comprehensive and systematic literature search was conducted across 3 major electronic databases: PubMed, Web of Science, and

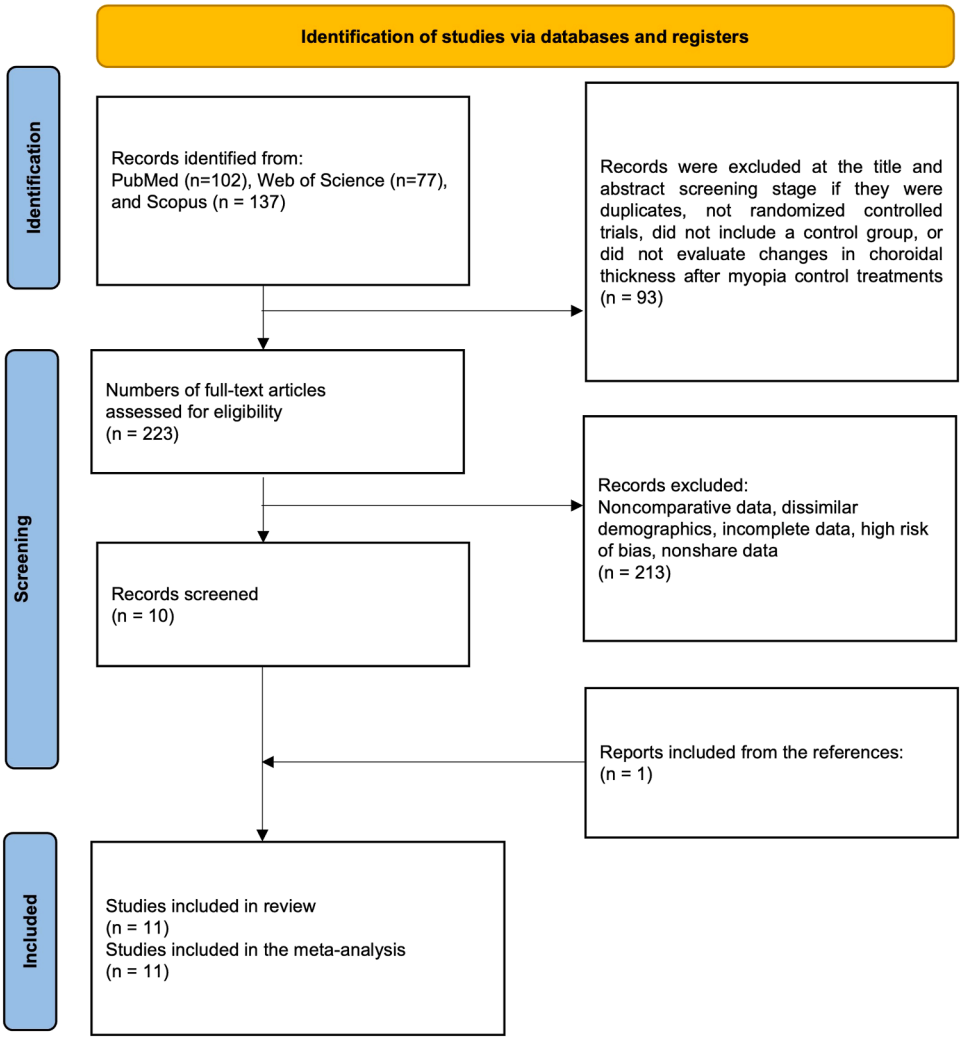

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Scopus, with no restrictions on publication date or language. To maximize completeness, the reference lists of all included articles were also manually screened to identify additional relevant studies not captured in the initial database search.

Search Methods for Identification of Studies

The search strategy combined controlled vocabulary and free-text terms related to myopia, choroidal morphology, and major myopia control interventions. Core search concepts included: "myopia," "axial length," "choroidal thickness," "subfoveal choroidal thickness," "choroidal vascularity," "orthokeratology," "atropine," "low-dose atropine," "defocus lenses," "multifocal contact lenses," and "myopia management," as well as imaging modalities such as "optical coherence tomography," "swept-source OCT," and "enhanced depth imaging." Full search strategies for each database are detailed in Additional File 2, available at www.ophthalmologyscience.org. Two reviewers (C.M.P. and A.P.O.) independently screened titles, abstracts, and full texts for eligibility, resolving discrepancies through discussion and consensus. No language restrictions were applied; studies published in languages other than English were translated and included when relevant data were available.

Data Extraction and Data Items

Two authors (A.-P.O. and C.M.P.) independently extracted data from all eligible RCTs. For each study, the following characteristics were recorded: first author, year of publication, country or region, study design, sample size per intervention group, mean participant age, treatment modality, treatment duration, methods used to measure ChT, and disclosure of conflicts of interest. Any discrepancies in data extraction or eligibility assessment were resolved through discussion and consensus, with no need for a third reviewer. Study management, including duplicate removal and tracking of eligibility decisions, was conducted using Rayyan (Rayyan Systems Inc, Qatar Computing Research Institute).

The primary variables extracted focused on changes in ChT, assessed by OCT, across different follow-up periods. Additional data were collected on treatment protocols (e.g., atropine dosage, lens type, OK design, or red-light therapy parameters), inclusion/exclusion criteria, and subgroup characteristics (e.g., baseline age, refractive error, axial length [AL]). These data were used to enable

subgroup and sensitivity analyses and to evaluate methodological heterogeneity across studies.

For atropine trials reporting multiple concentrations (0.01%, 0.025%, and 0.05%), each dose-specific arm was extracted and treated as an independent comparison within the meta-analysis, without pooling concentrations together.

To ensure consistency across OCT-derived outcomes, ChT was extracted exclusively from the subfoveal location; when studies reported ETDRS-grid data, the central 1-mm subfield was used. When both automated and manual/caliper measurements were available, the value corresponding to the study's primary predefined ChT outcome was extracted. Variability related to segmentation methods, examiner number, or device type was inherently controlled by the randomized parallel-group design of the included RCTs, as any measurement bias would affect treatment and control arms equally within the same study.

Methodological Quality and Risk of Bias Assessment

The methodological quality and risk of bias of the included RCTs were independently evaluated by 2 reviewers (C.M.P. and A.P.O.) using the Cochrane Collaboration's Risk of Bias tool, as implemented in Review Manager (RevMan, Version 5.4, The Cochrane Collaboration). This tool assesses 7 key domains of potential bias: random sequence generation, allocation concealment, masking of participants and personnel (performance bias), masking of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias. Each domain was judged as low, high, or unclear risk according to predefined criteria. Disagreements between reviewers were resolved through discussion and consensus. The overall results of the risk of bias assessment are summarized in Figure 2, with detailed domain-specific justifications provided in Additional File 3, available at www.ophthalmologyscience.org.

Assessment of Results

For continuous outcomes measured on the same scale, mean differences with 95% CIs were calculated. As all studies reported changes in ChT in micrometers (μm), no standardization across different scales was required. For dichotomous outcomes, odds ratios with corresponding 95% CI were computed when applicable. Statistical heterogeneity among studies was assessed using the I^2 statistic and interpreted as low (<25%), moderate (25%−50%), or high (>50%) heterogeneity. A fixed-effects model was applied when heterogeneity was not significant ($I^2 \leq 50\%$), while a random-effects model was used in cases of moderate or high heterogeneity. When necessary, missing or incomplete data were managed according to methodological guidance from the Cochrane Handbook for Systematic Reviews of Interventions.[33] All meta-analytic calculations and figure generation were conducted using Review Manager (RevMan, version 5.4, The Cochrane Collaboration).

Publication Bias

Potential publication bias was assessed by visually inspecting funnel plots generated with Review Manager for the primary outcome of ChT. Asymmetry in the funnel plots was interpreted as a possible indication of publication bias, suggesting the non-publication of smaller studies with null or inconclusive findings.

Additional Analyses

Sensitivity analyses were conducted to evaluate the robustness of the meta-analytic results by sequentially removing studies identified as highly influential or major contributors to heterogeneity in ChT outcomes. This approach allowed assessment of the impact of individual studies on pooled effect estimates and clarified the sources of heterogeneity, particularly at longer follow-up periods. All sensitivity analyses were performed using Review Manager, applying a random-effects model when moderate or high heterogeneity was detected.

Additionally, the certainty of evidence for each intervention was assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach,[34] considering risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. Inconsistency criteria explicitly accounted for substantial heterogeneity or limited follow-up in certain intervention groups. All assessments were independently performed by 2 reviewers, with discrepancies resolved through discussion and consensus.

Results

Study Selection

A total of 316 records were initially retrieved from PubMed (n = 102), Web of Science (n = 77), and Scopus (n = 137) (Fig 1). After removal of duplicates and screening of titles and abstracts, 93 records were excluded. The exclusion criteria at this stage included studies that were not RCTs, did not include a control group, or did not evaluate changes in ChT after myopia control treatments. Subsequently, 223 full-text articles were assessed for eligibility. Of these, 213 were excluded due to non-comparative data, dissimilar demographics, incomplete data, high risk of bias, or lack of shareable data. An additional study was identified through manual review of reference lists. In total, 11 studies met the inclusion criteria and were included in both the systematic review and the meta-analysis.[8,9,35–43]

Study Characteristics

Table 1 summarizes the main characteristics of the RCTs included in this meta-analysis, which investigated the effects of different myopia control interventions on ChT in pediatric populations across diverse regions, including China, Hong Kong, Ireland, and Australia. Sample sizes ranged from relatively small single-center studies with <40 participants to large multicenter trials enrolling >300 subjects. The mean age of participants varied from early childhood (approximately 8 years) to adolescence (up to 12 years).

All included studies employed a randomized controlled design and compared conventional single-vision correction or placebo with active myopia control modalities, such as low-concentration atropine (0.01%−0.05%), OK, highly or slightly aspherical lenslets, RLRL therapy, and low-intensity laser therapy. Treatment durations varied considerably, from short-term interventions lasting 1 month to long-term follow-up of up to 24 months. Choroidal thickness was consistently

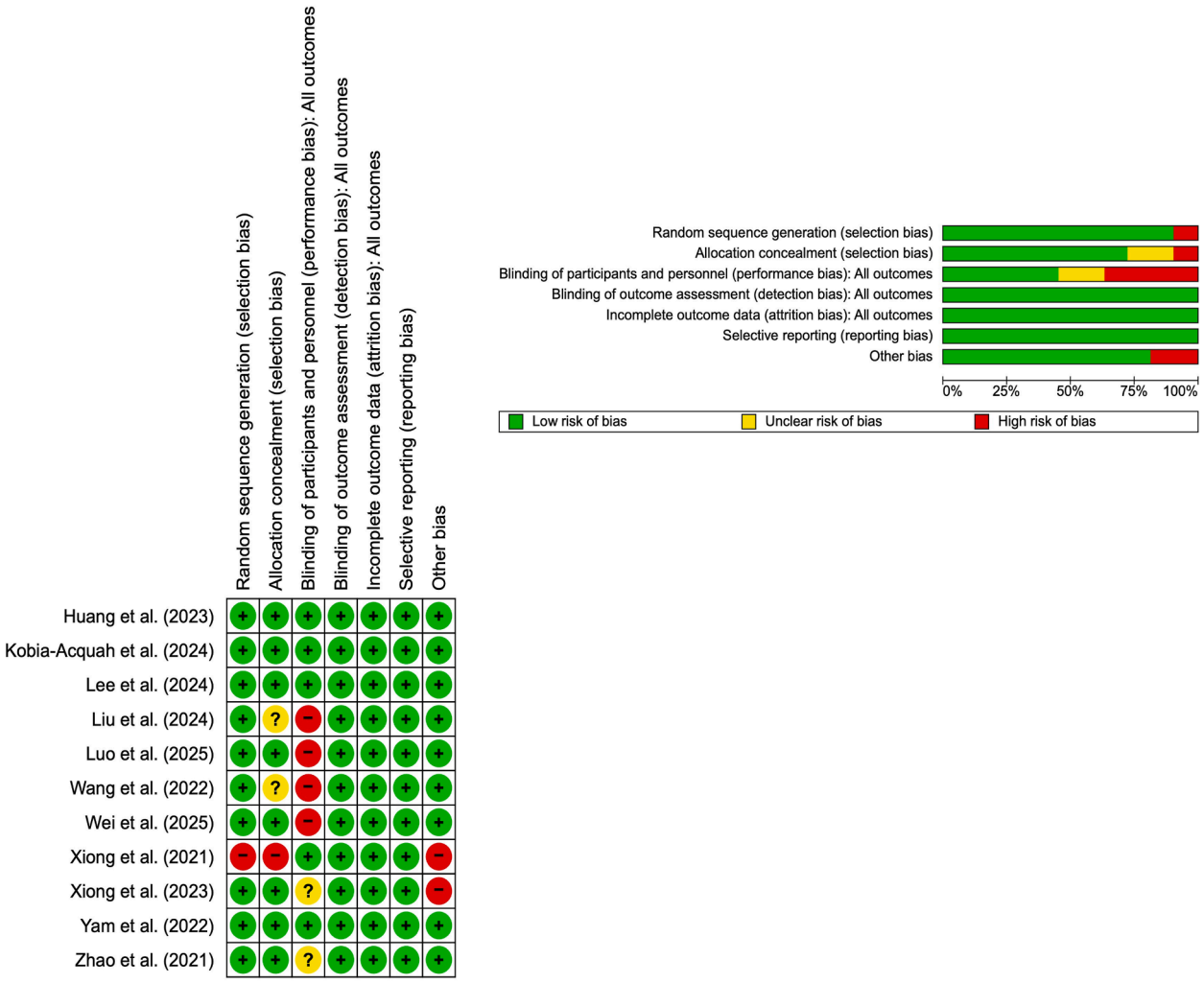

Figure 2. Risk of bias assessment (green = low risk; red = high risk; yellow = unknown) of 11 RCTs. RCT = randomized controlled trial.

assessed using OCT platforms, including swept-source OCT (Topcon Triton, DRI-OCT), spectral-domain OCT (Heidelberg Spectralis, Cirrus HD, RTVue XR Avanti), and enhanced depth imaging protocols, with several studies applying automated segmentation, ETDRS grid analysis, or image binarization methods. Measurements were typically performed under cycloplegia, and most studies reported standardized procedures for subfoveal and parafoveal regions.

Conflict of interest statements were reported across all studies, with none disclosing potential financial or proprietary interests.

Outcomes

Figure 3 presents the pooled results of RCTs evaluating repeated RLRL therapy on ChT compared with controls. Significant thickening was observed at both 1 month (mean difference = 18.7 μm) and 3 months (mean difference = 22.1 μm), with no evidence of heterogeneity. At 6 months, the effect remained significant (mean difference = 20.6 μm) with moderate heterogeneity (I^2 = 65%). A single 9-month study showed a larger effect (mean difference = 42.1 μm), while 3 trials at 12 months confirmed sustained thickening (mean difference = 31.1 μm) but with high heterogeneity (I^2 = 83%). Overall, RLRL therapy was associated with a robust thickening effect (mean difference = 24.1 μm, 95% CI: 19.8 to 28.5), although variability increased at longer follow-up durations.

Figure 4 presents the pooled analysis of RCTs assessing the effect of low-dose atropine on ChT compared with control groups. At 1 month, a significant increase was observed (mean difference = 10.3 μm, 95% CI: 6.02−14.58), while small or imprecise effects were reported at 3 months. At 4 and 6−8 months, pooled estimates showed modest increases (mean difference = 10.9 μm and 13.4 μm, respectively), though heterogeneity was high (I^2 = 82−90%). At 12 months, 4 trials confirmed a significant thickening effect (mean difference = 11.4 μm, 95% CI: 1.6−21.2), with consistent results also observed at 16 to 18 and 24 months.

Table 1. Baseline Characteristics of the 11 Included Studies

Author (Year)	Country	Study Design	Sample Size	Mean Age (Years)	Treatment/Modality	Follow-Up	Measurement Method	COI
Huang et al (2023)[35]	China	RCT	HAL: 54 SAL: 52 SVL: 68	HAL: 10.65 ± 1.15 SAL: 10.25 ± 1.19 SVL: 10.38 ± 1.21	HAL/SAL/SVL	24 months	SS-OCT (Topcon Triton); ETDRS grid; cycloplegic; manual/observer correction	No
Kobia-Acquah et al (2024)[36]	Ireland	RCT	Atropine: 126 Control: 61	Atropine: 11.93 ± 2.46 Control: 11.61 ± 2.15	Atropine 0.01% drops, 1x/day	24 months	SS-OCT (Topcon Triton), ETDRS grid, subfoveal, parafoveal, perifoveal regions	No
Lee et al (2024)[37]	Australia	RCT	Atropine: 101 Control: 47	Atropine: 11.2 ± 2.7 Control: 12.2 ± 2.5	0.01% atropine daily vs. placebo (2:1 ratio)	24 months	SD-OCT (Spectralis, EDI), image binarization (MATLAB), ETDRS grid, CVI analysis	No
Liu et al (2024)[38]	China	RCT	RLRL: 43 Control: 42	RLRL: 8.98 ± 1.31 Control: 8.95 ± 1.52	RLRL (2x/day, 3 min, 12 mo) vs. control	12 months	AL (IOL Master 700); SE (cycloplegic autorefraction/ retinoscopy); CT/vascular density (OCT/OCTA)	No
Luo et al (2025)[39]	China	RCT	Aspherical: 30 Spherical: 30	Aspherical: 10.77 ± 1.81 Spherical: 10.77 ± 1.81	Aspherical vs. spherical Ortho-K lenses (contralateral eyes)	12 months	IOLMaster (AL), Cirrus HD-OCT (CHT), MSR Topographer (RPRE)	No
Wang et al (2022)[40]	China	RCT	Atropine: 21 SVL: 19	Atropine: 9.9 ± 1.6 Control: 9.9 ± 1.9	Atropine 0.01% + SVL vs. SVL (control)	3 months	IOLMaster (AL), Spectralis SD-OCT (ChT), AngioVue OCTA (RT, RVD, FAZ, CCF)	No
Wei et al (2025)[41]	China	RCT	RLRL: 100 Control: 100	RLRL: 9.56 ± 1.97 Control: 8.97 ± 1.90	RLRL therapy (650 nm, 2x/day)	12 months	SD-OCT (RTVue XR Avanti)	No
Xiong et al (2021)[42]	China	RCT	OK: 81 LLLT: 74 Control: 74	OK: 10.9 ± 1.9 LLLT: 10.2 ± 2.4 Control: 10.3 ± 2.0	OK lens (overnight); LLLT (650 nm, 2 × 3 min/day); single-vision spectacles	6 months	AL (IOL Master, Zeiss); SFChT (OCT EDI); Cycloplegic SE; standard protocol	No
Xiong et al (2023)[9]	China	RCT	RLRL: 60 Control: 60	RLRL: 10.52 ± 1.53 Control: 10.37 ± 1.1	RLRL therapy (650 nm, 3 min/session, 2x/day, 5 days/week) vs. SVS (control)	12 months	SS-OCT (DRI-OCT Triton, Topcon), automated segmentation, macular choroidal thickness (mCT), cycloplegic, standardized protocol	No
Yam et al (2022)[8]	Hong Kong	RCT	316 (81: 0.05%, 80: 0.025%, 86: 0.01%, 69: switchover)	4–12 yrs	Atropine 0.05%, 0.025%, 0.01% daily vs. placebo	24 months	SD-OCT (Spectralis, EDI), manual segmentation (MATLAB), afternoon, cycloplegia, SFChT	No
Zhao et al (2021)[43]	China	RCT	OK: 36 Atropine: 42 Control: 37	OK: 10.33 ± 1.65 Atropine: 9.96 ± 1.03 Control: 9.73 ± 1.04	ACO (OK + 0.01% atropine), OK alone, 0.01% atropine alone, control (SV glasses)	1 month	SD-OCT (Heidelberg Spectralis EDI), AL by Lenstar LS 900, cycloplegia	No

ACO = atropine combined with orthokeratology; AL = axial length; ChT/CT = choroidal thickness; CCF = choriocapillaris flow; COI = conflict of interest; CVI = choroidal vascularity index; EDI = enhanced depth imaging; FAZ = foveal avascular zone; HAL = highly aspherical lenslets; HD-OCT = high definition OCT; IOL Master = intraocular lens master (biometer, Zeiss); LLLT = low-level laser therapy; MATLAB = Matrix Laboratory; OCT = optical coherence tomography; OCTA = OCT angiography; OK = orthokeratology; RCT = randomized controlled trial; RLRL = repeated low-level red-light; RPRE = relative peripheral refraction error; RT = retinal thickness; RVD = retinal vessel density; SAL = slightly aspherical lenslets; SD-OCT = spectral-domain OCT; SE = spherical equivalent refraction; SFChT = subfoveal choroidal thickness; SS-OCT = swept-source OCT; SVL = single-vision lenses; SVS = single-vision spectacles.

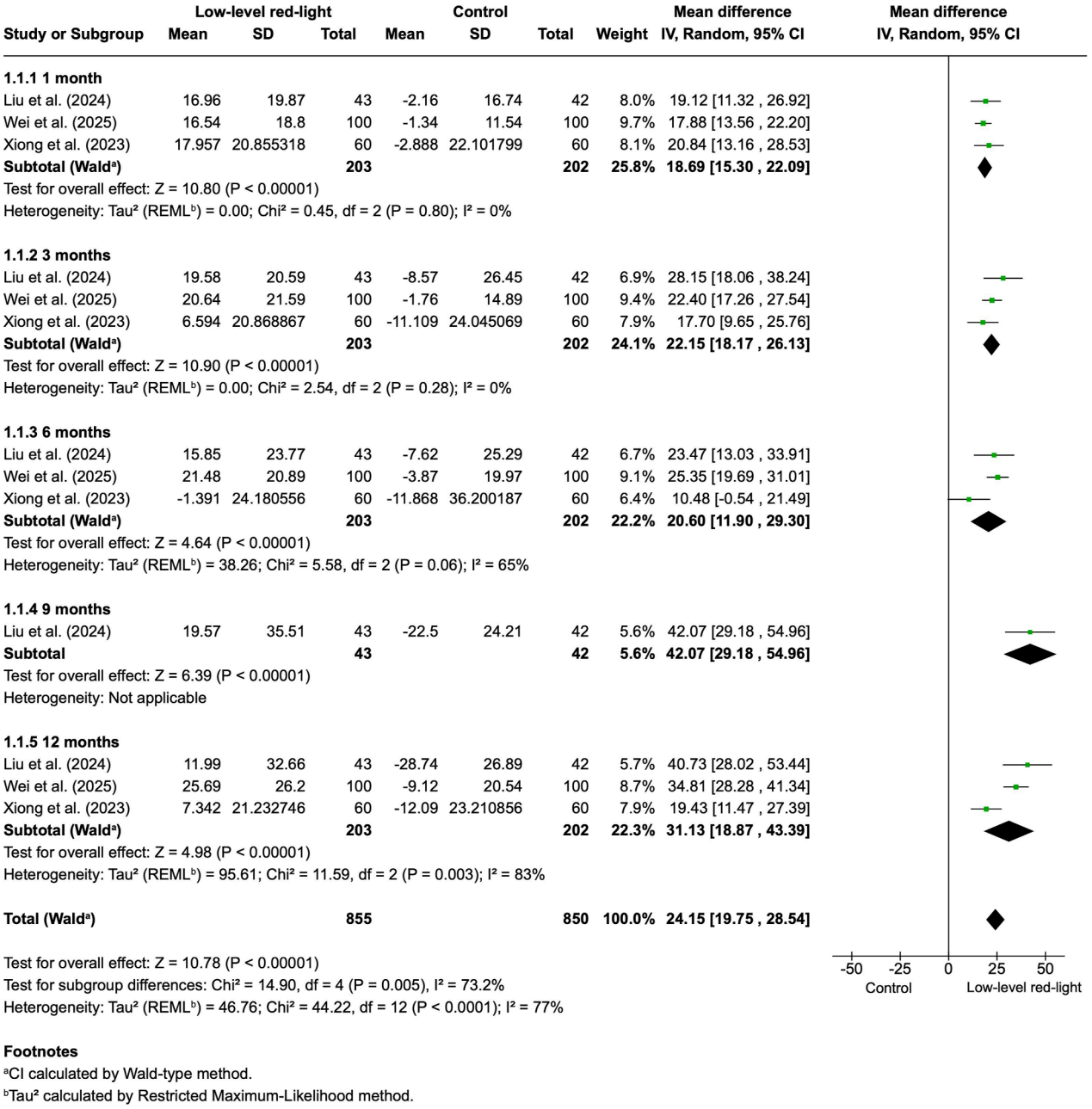

Figure 3. Forest plot of pooled choroidal thickness changes in myopic children treated with repeated low-level red-light therapy compared with control groups. [a]CI calculated by Wald-type method. [b]Tau^2 calculated by restricted maximum-likelihood method. Green squares represent the point estimates of individual studies, with the size of each square proportional to the study's weight in the meta-analysis. CI = confidence interval; REML = restricted maximum likelihood; SD = standard deviation.

In trials reporting multiple atropine concentrations, each dose-specific arm (0.01%, 0.025%, 0.05%) was extracted and included separately in the pooled analysis, without combining concentrations across arms.

The overall analysis across 2190 eyes demonstrated a significant increase in ChT with atropine (mean difference = 10.6 μm, 95% CI: 6.7−14.5; $P < 0.00001$). Nevertheless, substantial heterogeneity ($I^2 = 97\%$) suggests variability across study designs and populations.

Figure 5 presents the pooled analysis of RCTs evaluating the effect of spectacle lenses with aspherical or highly aspherical lenslets on ChT compared with SVL.

At 6 months, no significant differences were observed (mean difference = 8.7 μm, 95% CI: −6.3 to 23.7; $I^2 = 0\%$). At 12 months (n = 202), the pooled analysis indicated a significant increase in ChT with lenslets (mean difference = 15.3 μm, 95% CI: 0.4−30.2; $I^2 = 9\%$). At 18 months (n = 202), the effect remained significant (mean

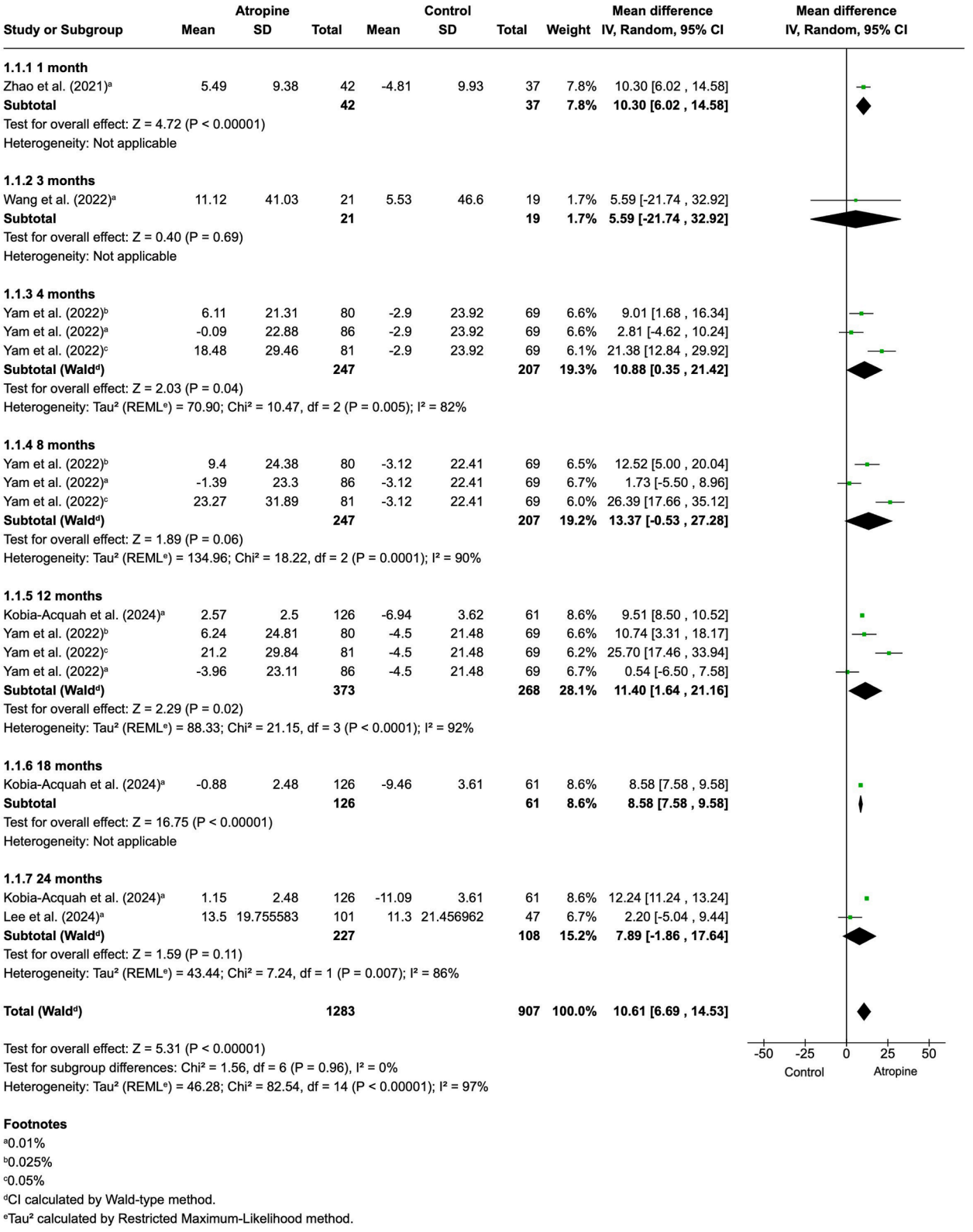

Figure 4. Forest plot of pooled choroidal thickness changes in myopic children treated with low-dose atropine compared with control groups. [a]0.01%; [b]0.025%; [c]0.05; [d]CI calculated by Wald-type method; [e]Tau^2 calculated by restricted maximum-likelihood method. Green squares represent the point estimates of individual studies, with the size of each square proportional to the study's weight in the meta-analysis. CI = confidence interval; REML = restricted maximum likelihood; SD = standard deviation.

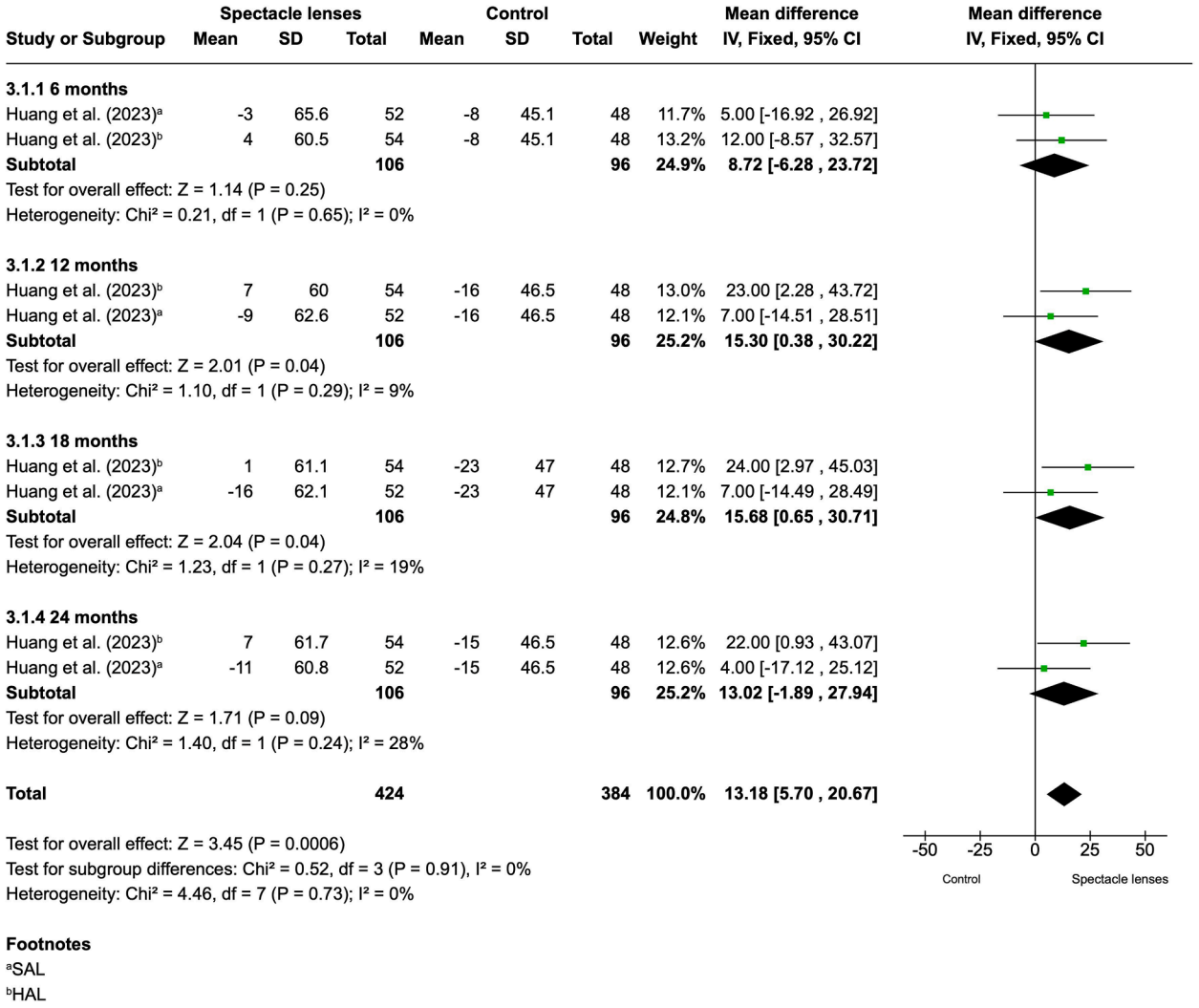

Figure 5. Forest plot of pooled choroidal thickness changes in myopic children treated with aspheric spectacle lenses compared with control groups. [a]SAL; [b]HAL. Green squares represent the point estimates of individual studies, with the size of each square proportional to the study's weight in the meta-analysis. CI = confidence interval; HAL = highly aspherical lenslets; SAL = slightly aspherical lenslets; SD = standard deviation.

difference = 15.7 μm, 95% CI: 0.6−30.7; I^2 = 19%). At 24 months (n = 202), the effect was smaller and not statistically significant (mean difference = 13.0 μm, 95% CI: −1.9 to 27.9; I^2 = 28%).

The overall pooled analysis across 808 eyes confirmed a significant increase in ChT with lenslet designs compared with controls (mean difference = 13.2 μm, 95% CI: 5.7−20.7; P = 0.0006), with no evidence of heterogeneity (I^2 = 0%).

These findings suggest that aspherical and highly aspherical lenslet spectacles produce a modest but significant thickening of the choroid, particularly at 12 and 18 months, although the effect appears to diminish by 24 months.

Figure 6 presents the pooled analysis of RCTs evaluating the effect of OK on ChT compared with control groups.

At 1 month, 2 studies (n = 215) showed a significant increase in ChT with OK (mean difference = 14.2 μm, 95% CI: 9.9−18.5; I^2 = 0%). At 3 months (n = 185), the pooled effect was not statistically significant (mean difference = 9.9 μm, 95% CI: −3.8 to 23.7; I^2 = 48%). At 6 months (n = 215), OK produced a significant thickening effect (mean difference = 15.6 μm, 95% CI: 1.3−29.8), although with moderate heterogeneity (I^2 = 74%). A single trial at 9 months (n = 30) and another at 12 months (n = 30) reported small, nonsignificant changes (mean difference = 5.9 μm and 5.5 μm, respectively).

The overall pooled analysis across 778 eyes confirmed a significant increase in ChT with OK compared with control

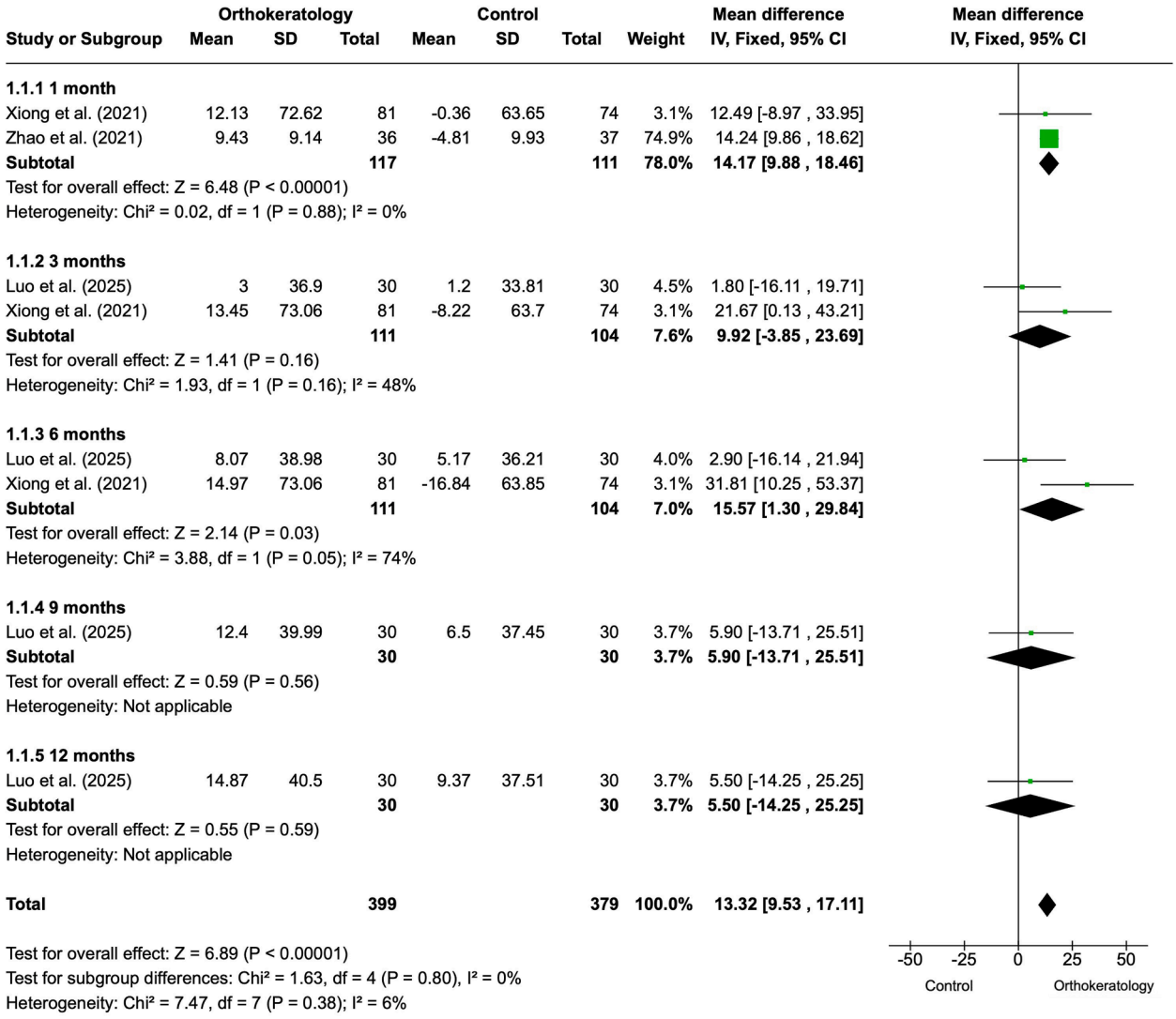

Figure 6. Forest plot of pooled choroidal thickness changes in myopic children treated with orthokeratology compared with control groups. Green squares represent the point estimates of individual studies, with the size of each square proportional to the study's weight in the meta-analysis. CI = confidence interval; SD = standard deviation.

(mean difference = 13.3 μm, 95% CI: 9.5−17.1; $P < 0.00001$), with minimal heterogeneity ($I^2 = 6\%$).

These results suggest that OK induces a consistent thickening effect on the choroid, most evident in the early months of treatment, though findings at longer follow-up are less conclusive.

Sensitivity Analysis

A sensitivity analysis was conducted by excluding the study by Xiong et al, [9] which was identified as a major contributor to heterogeneity in the pooled analysis of ChT with RLRL therapy (Fig 7). At 6 months, the removal of this study reduced heterogeneity from 65% to 0%, while the pooled mean difference remained statistically significant at 24.92 μm (95% CI: 19.9−29.9; $P < 0.00001$). Similarly, at 12 months, exclusion of Xiong et al lowered heterogeneity from 83% to 0%, with the pooled mean difference remaining significant at 36.0 μm (95% CI: 30.2−41.8; $P < 0.00001$).

Publication Bias

Publication bias was assessed using funnel plots for the primary outcome of changes ChT across the different myopia control interventions (Fig 8). The plots for atropine, OK, and lenslet spectacle appeared relatively symmetrical, suggesting little evidence of publication bias in these comparisons. In contrast, some degree of asymmetry was observed in the funnel plots for RLRL therapy, particularly at longer follow-up periods, which may indicate potential small-study effects. Overall, the funnel plots support the robustness of the meta-analytic findings, though results from subgroups with a limited number of trials should be interpreted with caution.

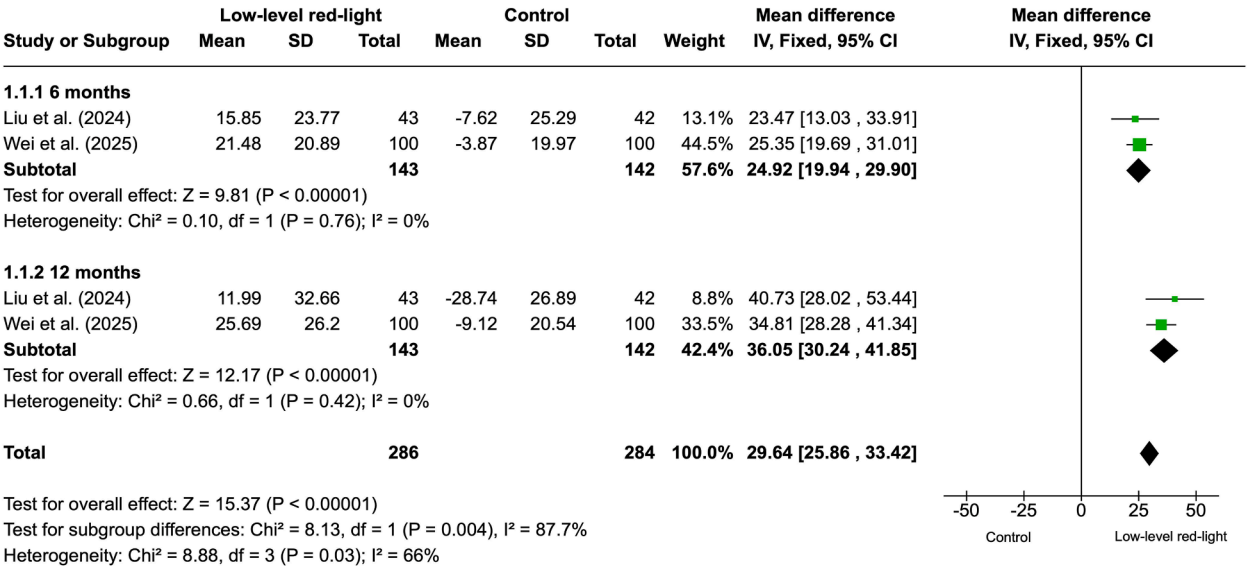

Figure 7. Sensitivity analysis of low-level red-light therapy versus control after exclusion of Xiong et al.[9] Green squares represent the point estimates of individual studies, with the size of each square proportional to the study's weight in the meta-analysis. CI = confidence interval; SD = standard deviation.

Grading of Recommendations, Assessment, Development and Evaluation

The Grading of Recommendations, Assessment, Development and Evaluation summary of findings for all major interventions is shown in Table 2. The certainty of evidence was rated as moderate for RLRL therapy and for low-dose atropine, due to serious inconsistency arising from substantial heterogeneity across trials, despite a consistent direction of effect. For spectacle lenses and for OK, the certainty of evidence remained high, as no serious concerns were identified in the key Grading of Recommendations, Assessment, Development and Evaluation domains. All interventions were classified as "critical" outcomes for clinical importance, reflecting the relevance of choroidal response in the context of myopia control.

Discussion

This systematic review and meta-analysis demonstrates that the myopia control interventions evaluated in the available RCTs, including RLRL therapy, low-dose atropine, OK, and highly aspherical lenslet spectacles, consistently induce a rapid, though often modest, increase in ChT in pediatric populations. The effect is most prominent during the early phase of treatment and is most marked with combination or high-dose pharmacological interventions, while optical monotherapies tend to produce more moderate and sometimes less durable changes. These results are largely consistent with recent controlled studies, although certain discrepancies in magnitude and duration emerge, which can be explained by differences in treatment regimen, population demographics, and imaging protocols.

Our pooled analysis indicates that all interventions included in this review lead to significant choroidal thickening compared with controls, especially in the first months of therapy. This is mirrored by the findings of Zhang et al,[44] who reported that both 0.05% atropine and its combination with dual-focus contact lenses induced robust choroidal expansion and transient axial shortening, with the effect of combination therapy sustained longer after discontinuation. Similarly, the study by Hao and Zhao[45] found greater subfoveal choroidal thickening in children receiving OK plus 0.01% atropine than in those on monotherapy and noted a plateauing effect after the initial month. The convergence of our results and these studies support the interpretation that pharmacological and optical interventions can act synergistically on choroidal morphology, with the earliest and largest changes observed in combination protocols. Several individual randomized trials have reported that greater short-term choroidal thickening is associated with reduced axial elongation, particularly in studies of high-dose atropine and OK.[10,46,47] However, this relationship cannot be inferred from our pooled analysis, as AL outcomes were not evaluated in this meta-analysis.

Mechanistically, our synthesis and the literature point toward a shared pathway. Most studies employing advanced OCT and image binarization indicate that choroidal thickening is driven by proportional expansion of both luminal (vascular) and stromal compartments, with minimal change in the choroidal vascularity index. This has been observed across modalities, including atropine, OK, and RLRL therapy,[44,46–48] suggesting that vascular engorgement and stromal fluid shifts are the dominant microstructural responses, rather than selective angiogenesis or remodeling. For example, Xu et al[47] showed that OK improves choroidal structure primarily through increased luminal area, and that children with greater baseline luminal area derive the most benefit in terms of axial growth control. The expansion of the luminal compartment, especially after RLRL therapy, appears to

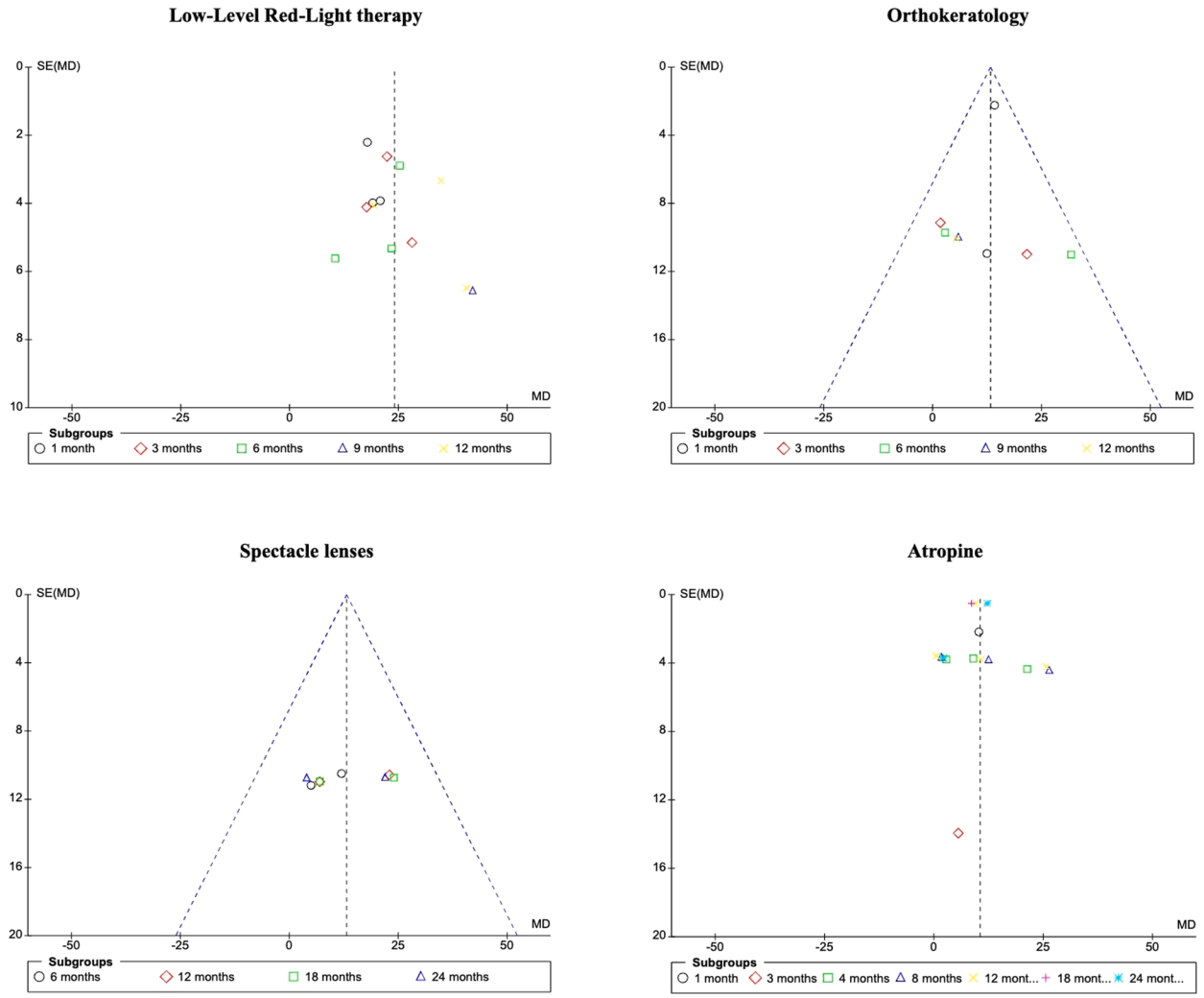

Figure 8. Assessment of publication bias. MD = mean difference; SE = spherical equivalent.

underpin the link between choroidal changes and slowed axial elongation.

The relatively pronounced and rapid choroidal thickening observed with RLRL therapy, however, warrants cautious interpretation. Although several trials report a robust structural response, the underlying mechanisms remain insufficiently understood and may not reflect the same physiological pathways involved in optical or pharmacological treatments. Some photobiomodulation studies have suggested that red-light exposure could transiently alter vascular tone or increase choroidal perfusion, and in certain experimental contexts may even trigger low-grade inflammatory or photochemical responses, although these mechanisms have not been demonstrated in current pediatric RLRL trials.[38,41] This raises the possibility that part of the early thickening may not represent a purely regulatory effect. Given that the long-term ocular safety profile of RLRL is not yet fully established, these findings should be interpreted with appropriate caution until additional mechanistic and safety data become available.

Despite broad agreement, some differences in magnitude, duration, and anatomical distribution of choroidal response were evident. Optical interventions such as multifocal contact lenses and aspherical lenslet spectacles produced significant but smaller and more homogeneous thickening, typically stable across macular regions and less sustained at longer follow-up.[44,49] The spectacle lens trials merit particular consideration because only 2 RCTs were available and they reported divergent short-term trends: one observed slight thinning during the first months, while the other documented modest thickening, although both interventions ultimately resulted in choroidal profiles that remained consistently thicker than those observed with SVL.[22,35] Several factors may explain these differences. The lenslet designs used across studies vary in the spatial arrangement and optical power of peripheral myopic defocus, which can influence the magnitude and speed of choroidal response.[49] In addition, baseline characteristics such as age, refractive error, and AL differ between samples and are known to modulate ChT and its short-

Table 2. Grading of Recommendations, Assessment, Development and Evaluation Assessment of the Quality of the Evidence and the Strength of the Recommendations

Certainty Assessment							No. of Patients		Effect			
No. of Studies	*Study Design*	*Risk of Bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Other Considerations*	*[Intervention]*	*[Comparison]*	*Relative (95% CI)*	*Absolute (95% CI)*	**Certainty**	**Importance**
Low-level red-light												
5	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	205/407 (50.4%)	202/407 (49.6%)	OR 10.61 (6.69 to 14.53)	416 more per 1000 (from 372 more to 438 more)	⨁⨁⨁◯ Moderate*	CRITICAL
Atropine												
2	Randomized trials	Not serious	Serious†	Not serious	Not serious	None	537/770 (69.7%)	233/770 (30.3%)	OR 13.18 (5.70 to 20.67)	549 more per 1000 (from 409 more to 597 more)	⨁⨁⨁◯ Moderate†	CRITICAL
Spectacle lenses												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	106/202 (52.5%)	96/202 (47.5%)	OR 13.18 (5.70 to 20.67)	447 more per 1000 (from 362 more to 474 more)	⨁⨁⨁⨁ High	CRITICAL
Orthokeratology												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	150/291 (51.5%)	141/291 (48.5%)	OR 13.32 (9.53 to 17.11)	442 more per 1000 (from 415 more to 457 more)	⨁⨁⨁⨁ High	CRITICAL

CI = confidence interval; OR = odds ratio.
*The repeated low-level red-light trials showed substantial heterogeneity at later follow-up points, with $I^2 = 65\%$ at 6 months and $I^2 = 83\%$ at 12 months, indicating marked variability in effect magnitude across studies despite a consistent direction of benefit. This heterogeneity was judged as serious inconsistency, leading to a 1-level downgrade in certainty.
†The atropine trials also demonstrated considerable heterogeneity in effect sizes across studies. This was judged as serious inconsistency, resulting in a 1-level downgrade in certainty.

term plasticity.[6,28] Methodological variations, including cycloplegia, the timing of OCT acquisition, accommodation demand, and diurnal fluctuations, represent further sources of variability.[23,27,28] Because pediatric ChT is highly sensitive to these factors, minor differences in imaging protocols may translate into apparent discrepancies in early choroidal behavior. Importantly, both trials converged on similar functional outcomes, showing reduced axial elongation relative to SVL despite the divergent initial choroidal pattern. This suggests that short-term thinning does not necessarily contradict a positive treatment effect and that choroidal adaptation to spectacle lens optics may follow different temporal dynamics before stabilizing into a thicker profile. Collectively, these considerations offer a plausible explanation for the conflicting early findings while supporting the overall interpretation of a modest but biologically coherent choroidal response to lenslet-based spectacle interventions.

In contrast, atropine's effect is both dose-dependent and reversible; higher concentrations produce pronounced thickening, while prolonged low-dose use may result in a loss of effect or even thinning.[10,46] Moreover, the substantial heterogeneity observed across atropine trials indicates that its choroidal response should be interpreted with caution, as differences in dosage, follow-up duration, cycloplegia protocols, and OCT timing likely contribute to the variability in effect size. The marked variability reported in the Yam studies[8,50] also suggests the influence of several protocol-related factors. Although these trials applied relatively tight visit schedules, differences in the timing of OCT acquisition relative to drop instillation, the degree of pupil dilation at each visit, and variations in compliance across subgroups could all affect short-term choroidal measurements. Additionally, their data sets included slightly different baseline characteristics and study arms with variable retention, which may further amplify fluctuations in early choroidal response. Together, these methodological and population-level differences likely account for the inconsistent effect estimates observed in atropine RCTs. Orthokeratology exhibits a rapid early increase that attenuates over time, as also seen in our meta-analysis, and is most effective in specific patient subgroups.[47]

In addition to protocol-related variability, differences in OCT technology likely contributed to between-study heterogeneity. Swept-source OCT systems provide deeper choroidal penetration, improved signal stability, and more reliable delineation of the choroid−scleral interface compared with spectral-domain platforms, which may underestimate thickness in eyes with greater pigmentation or lower reflectivity.[51,52] These devices also differ in axial resolution, scan speed, light source wavelength, and segmentation algorithms, leading to systematic inter-instrument discrepancies that can reach 20−30 μm, particularly in pediatric eyes.[52,53] Furthermore, ChT is highly sensitive to cycloplegic status, accommodation demand, and diurnal variation, factors that were inconsistently controlled across trials and can individually induce short-term fluctuations of 15−35 μm.[54] Variation in these parameters affects each instrument's sensitivity and repeatability and likely contributes to the heterogeneity observed in pooled estimates, particularly in atropine and red-light subgroups. Although quantifying the independent contribution of each imaging factor was not feasible with available data, their combined influence should be acknowledged when interpreting between-study variability.

In addition, because OCT-derived choroidal measurements are highly sensitive to methodological variation, we extracted ChT values using standardized criteria whenever possible. Only subfoveal ChT or the central 1-mm ETDRS field was included to ensure anatomical consistency across studies. When multiple measurement approaches were reported (e.g., automated segmentation vs. manual calipers, single vs. dual examiners), we extracted the value corresponding to the primary outcome defined by each RCT. Although differences in segmentation method, examiner variability, and OCT platform undoubtedly contribute to between-study heterogeneity, these factors are constant within each trial, meaning that treatment and control groups are measured under identical conditions. Therefore, while methodological variability may increase heterogeneity at meta-analytic level, it is unlikely to bias the direction or internal validity of the treatment effects derived from within-trial comparisons.

Further context is provided by the recent International Myopia Institute "Dynamic Choroid" review, which highlights both the physiological complexity of the choroid and the substantial limitations of OCT-derived ChT measurements.[55] The International Myopia Institute report emphasizes that short-term choroidal changes induced by optical, pharmacological, or environmental stimuli do not reliably predict long-term axial elongation, and that the mechanistic basis of these rapid structural shifts remains incompletely understood. It also underscores the high sensitivity of ChT to segmentation variability, diurnal fluctuations, accommodation, and device-related differences, reinforcing that ChT should be interpreted as a dynamic structural marker rather than a validated biomarker of treatment efficacy.

The findings must be interpreted in the context of several limitations. Most included RCTs were conducted in East Asian populations, potentially limiting generalizability to other ethnic groups. Importantly, ethnic and environmental factors may influence both baseline choroidal structure and its responsiveness to myopia control treatments. Evidence from longitudinal cohorts and defocus experiments shows that baseline ChT, short-term plasticity, and the magnitude of choroidal modulation vary with age, refractive status, and the rate of myopic shift.[6,7,14,28] East Asian children, who generally exhibit thinner choroids and faster axial elongation, may therefore display more pronounced or accelerated choroidal responses compared with populations with slower progression. These regional differences in biology and environment suggest that the magnitude and timing of choroidal changes observed in the included RCTs may not fully extrapolate to other

ethnic groups. The heterogeneity in protocols, imaging techniques, and timing of choroidal assessment could influence effect size and direction, and most studies had relatively short follow-up, preventing robust evaluation of the long-term durability and clinical significance of choroidal changes. Few studies provided granular data on choroidal substructure or detailed subgroup analyses by baseline characteristics, and the meta-analysis was based on aggregate rather than individual participant data. Although our review applied rigorous risk of bias assessment and sensitivity analyses, publication bias and selective reporting, especially for newer modalities like RLRL, cannot be fully excluded. Nevertheless, this meta-analysis provides a comprehensive and up-to-date synthesis of the impact of current myopia control strategies on choroidal morphology, strengthened by prospective registration, independent review, and quantitative methodology. The convergence of results across diverse interventions and populations supports the generalizability of the conclusions and reinforces the value of choroidal imaging as a potential adjunct marker for early treatment response.

Future research should prioritize large-scale, multiethnic randomized trials with standardized and detailed choroidal imaging protocols, longer-term follow-up, and advanced analysis of substructural changes. There is also a need to clarify the prognostic value of baseline choroidal features and to establish whether monitoring ChT and subcompartments can guide personalized treatment strategies. Ultimately, integrating choroidal imaging into routine practice, alongside AL monitoring, could enhance the precision of myopia management and improve outcomes for children at risk of progressive myopia.

Conclusions

This systematic review and meta-analysis show that the myopia control interventions for which RCTs reporting ChT outcomes are available (including RLRL therapy, low-dose atropine, OK, and aspherical lenslet spectacles) produce early and measurable increases in ChT in children and adolescents with myopia. The choroidal response tends to be more noticeable in the initial months of treatment. Pharmacological or combined approaches often show the largest short-term changes.

These findings describe the pattern and timing of choroidal modulation. However, they do not determine whether these changes reflect or predict treatment efficacy, because clinical outcomes such as axial elongation were not analyzed in this review. The variability seen in atropine studies also indicates that the magnitude and stability of its choroidal effect should be interpreted with caution.

Several studies report changes in stromal and vascular components, but current evidence is not sufficient to define a common physiological mechanism. These observations should be viewed as preliminary. Although there was some heterogeneity in protocols and populations, the overall consistency of choroidal changes highlights the need for further investigation.

Future research should include more diverse populations and longer follow-up. It is also important to examine the long-term relevance of choroidal remodeling and to explore whether baseline choroidal features have prognostic value. Large randomized trials that combine choroidal metrics with clinical outcomes are essential for understanding the role of these structural changes in pediatric myopia.

Footnotes and Disclosures

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No animal subjects were used in this study.

Authors' Contributions

Conception and design: Martinez-Perez, Oliveira

Analysis and interpretation: Martinez-Perez, Oliveira

Data collection: Martinez-Perez, Oliveira

Obtained funding: Martinez-Perez, Oliveira

Overall responsibility: Martinez-Perez, Oliveira

Abbreviations & Acronyms:
AL = axial length; **ChT** = choroidal thickness; **CI** = confidence interval; **OK** = orthokeratology; **RCT** = randomized controlled trial; **RLRL** = repeated low-level red-light; **SVL** = single-vision lenses.

Keywords:
Choroidal thickness, Myopia control, Optical coherence tomography.

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